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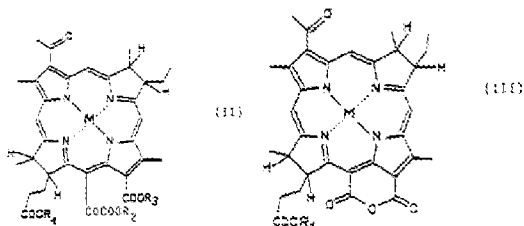
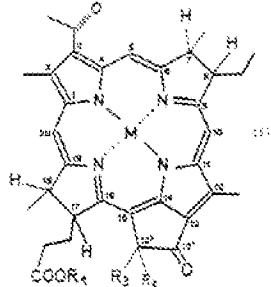
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(54) Modified Bacteriochlorophylls, a Method for Their Preparation and their Use

(57) Described are modified bacteriochlorophylls of the
general formula I, II or III



where

M denotes a hydrogen or a metal atom,

R₁ denotes an oligooxyethylene glycol residue or a
residue of an unbranched or branched... [sic]

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Specification

The invention relates to modified bacteriochlorophylls, a method for their preparation and their use for preparing agents for the diagnosis or treatment of tumors.

The selective accumulation of porphyrins and related compounds in tumors has been of great interest to the medical profession for some time. On the one hand, these pigments are suitable, owing to their fluorescence, for diagnosis, in particular also for early diagnosis, of superficially accessible tumors—thus, for so-called luminescence diagnosis. On the other hand, since the pigments participate in the photosensitized generation of singlet oxygen, these pigments can be used for a selective destruction of tumor tissues—thus, for so-called phototherapy (cf. R. V. Benasson et al., *Primary Photo-Processes in Biology and Medicine*, Plenum, New York, 1985; C. J. Gomer, *Photodynamic Therapy*, Special Edition *Photochem. Photobiol.*, Volume 46, No. 5 (1987); J. D. Spikes et al., in H. Scheer, *The Chlorophylls*, CRC Press, Boca Raton, 1991, page 1181).

In the clinical application of said compounds, the following aspects, among others, are important:

1. The accumulation of compounds in the body of the patient should occur with a maximum selectivity for the bonding in/to transformed target cells or cell layers.
2. The toxicity of the compounds under normal conditions should be low; however, their phototoxicity during use in phototherapy should be high.
3. The time, in which the compounds accumulate after application at the desired sites, should be defined and controllable.
4. After treatment of the patient, the applied compounds should be rapidly decomposed into physiologically harmless metabolites.
5. The compounds should have an intensive light absorption in such spectral ranges, in which the endogenic pigments do not absorb or do not become active elsewhere.
6. The compounds should absorb in a spectral range having maximum long waves in order to keep the light scattering low and to reach the greatest possible penetration depth of the light during the phototherapy, so that even tumors at lower depths can be detected.
7. The compounds should be readily soluble and adjustable in the body fluids.
8. For the corresponding spectral range there should be suitable light sources of corresponding size, intensity and ease of handling.

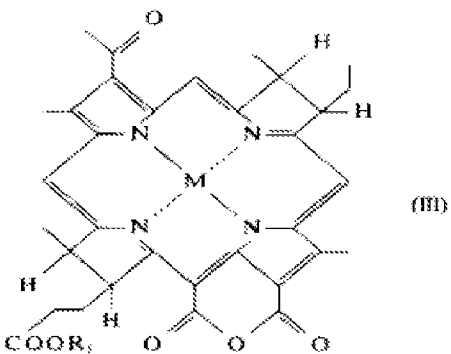
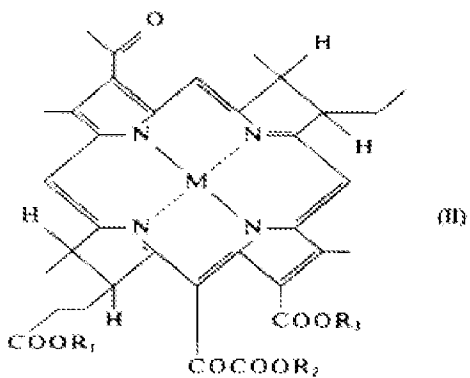
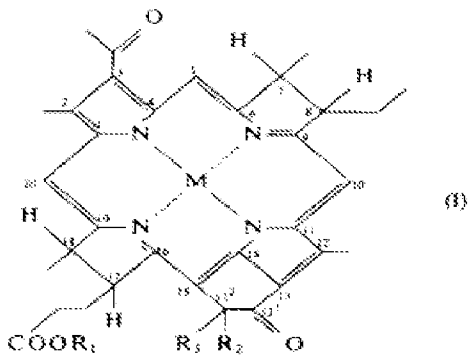
Due to these criteria the interest in chlorophyll derivatives has increased recently (cf. J. D. Spikes in H. Scheer, loc. cit.; R. Cubeddu et al. and E. M. Beems et al. in C. J. Gomer, loc. cit.). These derivatives have a comparatively low auto-toxicity, are highly phototoxic, have intensive long wave absorption around 670 nm and are relatively easy to decompose. However, they have the drawback that they are chemically quite unstable. Furthermore, the result is that the possibilities of modifying these derivatives in order to fulfill the other aforementioned criteria is significantly constrained (cf. H. Scheer in D. Dolphin, *The Porphyrins*, Volume II, Chapter 1, Academic Press, New York, 1978; H. Scheer, *The Chlorophylls*, CRC Press, Boca Raton, 1991).

Therefore, there exists a pressing need for reaction paths that allow certain parts of such molecules to be modified in a variety of ways. In this respect the current focus of interest is on chlorophyll derivatives, in which the isocyclic ring V is open, because these compounds are comparatively stable. Furthermore, they have already been clinically tested.

However, the past tested compounds are still unsatisfactory with respect to fulfilling the aforementioned criteria.

Therefore, the invention is based on the technical object of providing a method, by means of which a plurality of different compounds, which exhibit, on the one hand, some of the good properties of the known green chlorophylls in the field of tumor diagnosis and treatment, yet exhibit, on the other hand, improvements in many aspects—for example, in their infrared absorption properties—are accessible in a technically simple and cost-effective way.

This technical object is achieved by the invention by means of modified bacteriochlorophylls of the general formula I, II, or III



where

M denotes a hydrogen or a metal atom,

R₁ denotes an oligooxyethylene glycol residue or a residue of an unbranched or branched aliphatic or a cycloaliphatic, optionally halogenated, alcohol having at least 3 carbon atoms or a residue of a hydroxylated amino acid, a sugar alcohol, a hydroxylated lipid, a linear polyol, an amino alcohol, a hydroxycarboxylic acid, a nitroxide group containing alcohol, an alcohol containing chromophoric residues or an alkylbenzyl alcohol,

R₂ denotes a hydrogen atom, a hydroxyl group or a residue of the general formula -COOR₄, where R₄ denotes an alkyl or cycloalkyl residue having 1 to 12 carbon atoms, and

R₃ denotes a hydrogen atom, a hydroxyl group or an alkyl or alkoxy residue having 1 to 12 carbon atoms,

where R_2 and R_3 can also be identical.

The modified bacteriochlorophylls according to the invention are different from the bacteriochlorophylls that are used

as the parent compounds in that the propionic acid side chain, which is bonded to the C-17 carbon atom of the bacteriochlorophyll molecule, is subjected to a transesterification. The essential advantage of the modified bacteriochlorophylls according to the invention lies in the fact that the alcohol component in this propionic acid ester group can be selected in a variety of different ways. For example, by introducing a hydrophilic alcohol component it is possible to raise the solubility of the modified bacteriochlorophyll in water. In other cases it is possible to increase the ability of the molecules of the bacteriochlorophylls to form aggregates with each other and, thus, to increase the absorption wavelengths and the sensitization to light. Furthermore, it is possible with a suitable choice of the alcohol component to intensify the selectivity of the modified bacteriochlorophylls for detecting the target cells by way of condensations with other components, like physiologically important sugar alcohols or antibodies. Even the biological decomposition of modified bacteriochlorophylls can be controlled by the choice of the said alcohol component.

The preferred modified bacteriochlorophylls according to the invention are those, for which M denotes a magnesium, zinc, nickel, copper or tin atom in the general formula I, II or III. However, the compounds according to the invention can also be present in the form of metal-free bases.

If in the modified bacteriochlorophylls according to the general formula I, II or III the R_1 residue denotes an oligooxyethylene glycol residue, then such a residue having 4 to 10 carbon atoms or a tetra-bis-decaoxyethylene glycol residue—in particular, a pentaoxyethylene glycol residue—is preferred.

If R_1 is an aliphatic or cycloaliphatic, optionally halogenated, alcohol residue, then it has preferably 3 to 20—in particular, 3 to 12—carbon atoms.

Suitable halogens in the halogenated, alcohol residues are fluorine, chlorine, bromine and iodine, where fluorine is preferred. The latter has the special property that it can detect in a selective way in the NMR spectroscopy.

Furthermore, the modified bacteriochlorophylls that are especially advantageous are those, for which in the general formula I, II or III the R_1 residue denotes a residue of a fluorinated alcohol—in particular, a fluoroethyl or trifluorobutyl group—or a sorbityl, O-serinyl, aminohexyl or pentaoxyethylene glycol group.

If in the general formula I, II or III the R_1 residue denotes an alkylbenzyl alcohol residue, then the alkyl residue has preferably 1 to 10—in particular, 1 to 5—carbon atoms.

Examples for the case that the R_1 residue denotes an alcohol residue with a chromophoric molecular content are the alcohol residues having a pyrene, eosin or methylene blue structure.

If in the general formula I or II the R_2 residue denotes a residue of the general formula $-\text{COOR}_4$, then R_4 contains preferably 1 to 5 carbon atoms as the alkyl or cycloalkyl residue and is, in particular, the methyl group.

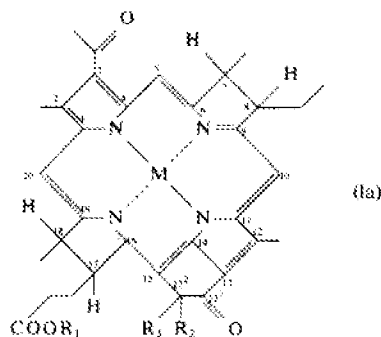
If in the general formula I or II the R_3 residue denotes an alkyl or alkoxy residue, then it has preferably 1 to 12 carbon atoms and is, in particular, a methyl group.

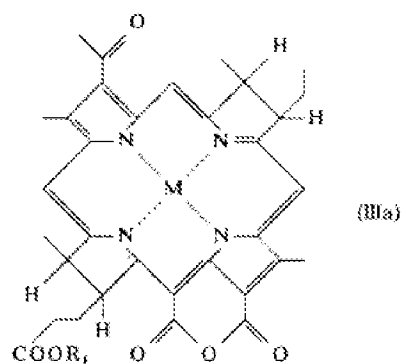
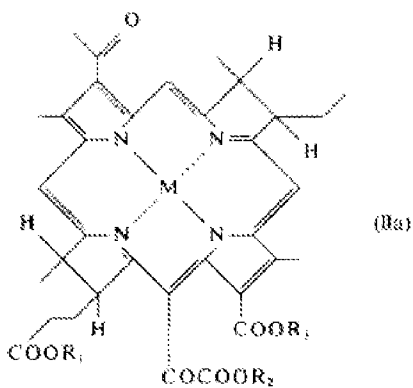
Especially valuable are also such modified bacteriochlorophylls, for which in the general formula I or II the R_3 residue denotes a hydroxyl group.

The modified bacteriochlorophylls can also be present in a structural form, in which two or—to the extent that it is sterically possible—more bacteriochlorophyll residues are esterified with a bivalent or polyvalent alcohol.

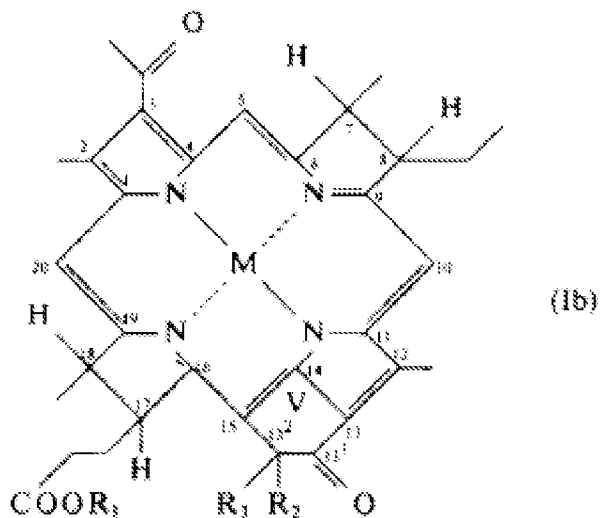
If in the general formulas I, II or III the R_1 residue denotes a polyol in the form of diol, then it has preferably 2 to 12—in particular, 2 to 6—carbon atoms.

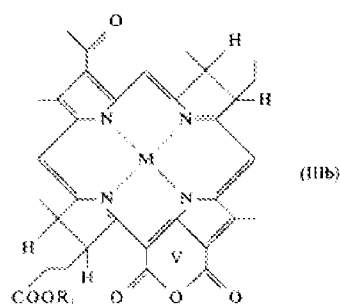
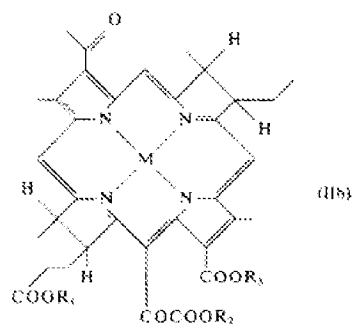
The invention also relates to a method for preparing modified bacteriochlorophylls of the general formula Ia, IIa or IIIa





where M, R₁, R₂ and R₃ have the same meaning as disclosed in claim 1, but in addition R₁ can also denote a methyl, ethyl, ethylene glycol or phytyl group or a residue of a diterpene alcohol, characterized in that a bacteriochlorophyll of the general formula Ib, IIb or IIIb





where M, R₁, R₂ and R₃ have the same meaning as given above for the general formulas Ia, IIa and IIIa, and where V in the general formulas Ib and IIIb denotes a ring in the total structure of the bacteriochlorophyll, in the presence of a base as well as in the presence or absence of an inert solvent and/or a stoichiometric excess of one of the two reaction partners with at least one alcohol in the form of phytol or oligooxyethylene glycol or an unbranched or branched aliphatic or cycloaliphatic, optionally halogenated, alcohol, or in the form of a hydroxylated amino acid, a sugar alcohol, a hydroxylated lipid, a linear polyol, an amino alcohol, a hydroxycarboxylic acid, a nitroxide group containing alcohol, an alcohol containing chromophoric residues, an alkylbenzyl alcohol having 1 to 12 carbon atoms in the alkyl residue or a diterpene alcohol on the propionic acid residue, which is bonded to the carbon atom C-17 of the bacteriochlorophyll, is transesterified and the resulting modified bacteriochlorophyll is isolated from the reaction mixture.

In the method according to the invention, a transesterification takes place on the C-17 propionic acid side chain of the parent compound. Preferably at the same time the ring V in the compounds of the general formulas Ib and IIIb is protected or structured in such a manner that its enolization is suppressed. This is the case, for example, when the parent compound that is used is a pyro-bacteriochlorophyll, in which the R₂ and R₃ residues denote hydrogen atoms; or 13²-hydroxy or 13²-alkoxy-bacteriochlorophylls. It is self-evident that other possibilities of protecting the ring V that are known to those skilled in the art may be considered.

The parent compounds that may be used may also be such bacteriochlorophylls, in which the ring V is open, as shown in the general formula IIb. The compounds of this type include, for example, bacteriochlorine e₆.

The parent compounds of the method according to the invention are easily accessible. For example, the bacteriochlorophyll a, 13²-hydroxy-bacteriochlorophyll a, pyro-bacteriochlorophyll a, 13²-hydroxy-bacteriochlorophyll a-ethyl ester, 13²-hydroxy-bacteriochlorophyll a-pentaoxyethylene ester, bacteriochlorophyll a-methyl ester and ethylene glycol-bis-bacteriochlorophyll as well as esters from diterpene alcohols and bacteriochlorophylls are known and to some extent can also be obtained as a natural substance. In principle, it suffices if any kind of bacteriochlorophyll is available, because all other derivatives that fall under the aforementioned general formulas can be prepared according to the method of the invention.

That means that the method according to the invention enables, on the one hand, the preparation of novel compounds that are defined by the general formulas I, II and III. On the other hand, however, this method can also be used to prepare known compounds. The aforementioned general formulas Ia, IIa and IIIa of the final substances of the method according to the invention comprise both the novel substances of the general formulas I, II and III as well as the known modified

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bacteriochlorophylls. In other words, all of these compounds—whether novel or known—can be converted into one another by means of the method according to the invention. This signifies an important advantage of the method, because it provides a plurality of different active substances, from which many diagnostic agents and drugs in the area of tumor control can be prepared. Since these active substances are so different, it is also possible to adjust, as desired, the properties of these agents.

The parent compounds that can be used for the method according to the invention may also be the metal-free bases of the bacteriochlorophylls—that is, the bacteriopheophytins.

The preferred metal-containing bacteriochlorophylls that are used are those, whose metal complex bond is relatively strong and that are, therefore, comparatively stable to demetalation. This applies, for example, to bacteriochlorophylls of the general formula Ib, IIb, or IIIb, where M denotes a magnesium, zinc or nickel atom. In particular, it is surprising that the magnesium and zinc complexes are very stable in the alkaline medium of the method according to the invention and only seldom lead to decomposition or side reactions.

The method according to the invention can be carried out under basic conditions. The bases that can be used are preferably a hydroxyl ion-forming compound, a Lewis base or an organic base—for example, a bicyclic amine. In particular, an alkali metal hydroxide, like sodium or potassium hydroxide, and tertiary amines, like diazabicycloundecane, are preferred as bases. The basicity of the reaction mixture corresponds to a pH value of at least 8.

The method according to the invention can be carried out in the presence or absence of a solvent. If a solvent is used, then it is present preferably in the form of a stoichiometric excess of the alcohol compound. It can be successfully applied, for example, in the case of methanol, ethanol and 4,4,4-trifluorobutane-1-ol.

A preferred example of an isolated solvent is dioxan.

The transesterification temperature is normally at room temperature, but in isolated cases may also drop below or rise above room temperature.

The transesterification time ranges in general from a few minutes to about an hour.

Since in the method according to the invention the bacteriochlorophylls or the modified bacteriochlorophylls can be converted into one another in an almost arbitrary manner—that is, each of these compounds can be the parent substance or the final substance—the definitions of the residues coincide, on the one hand, with the general formulas Ia, IIa, and IIIa and, on the other hand, with the general formulas Ib, IIb, and IIIb. It is obvious that this coincidence does not hold true for each individual reaction.

In conjunction with the compounds according to the invention and the method according to the invention only the standard structural formulas are given for the respective substances for the sake of simplification. However, it is apparent that these substances also exist in the form of different stereoisomers and are usually present as an epimeric mixture. This mixture can be separated chromatographically—for example, on silica gel. Therefore, the invention comprises both the epimeric mixtures as well as also the individual epimers.

The modified bacteriochlorophylls that are obtained according to the method of the invention have the advantage over the compounds that are currently used in tumor diagnostics and therapy that they fulfill to a high degree the criteria 1 to 7 listed in the introductory part. In addition, they are especially valuable in that they exhibit, as compared to the chlorophyll derivatives, an absorption that is located far in the long wave range (up to approximately 800 nm). The method according to the invention makes it possible to access the modified bacteriochlorophylls in a very easy and cost-effective way. Furthermore, they can be isolated with a variety of alcohol components.

The inventive compounds, of which the ester group contains a fluorinated alcohol residue, are especially suited for nuclear magnetic resonance diagnostics. The inventive compounds with alcohol residues that contain the nitroxide groups are especially suited for electronic spin resonance diagnostics.

The modified bacteriochlorophylls that are prepared according to the invention are medicinal active ingredients and are used for the preparation of agents for the diagnosis or treatment of tumors. In this respect these compounds are combined with adjuvants in the conventional way in order to obtain a diagnostic agent or drug that is tailored to the various requirements, like the mode in which the drug is administered to the patient.

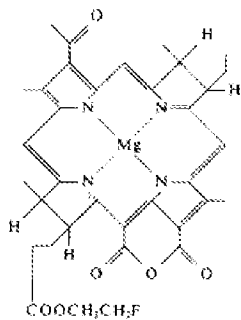
Specific examples of the modified bacteriochlorophylls that are prepared according to the invention are given below. Of the compounds I to XII that are listed in the table, the compounds I, II, III, IV, XI and XII are known substances. The compounds I, II and III are often used as the parent substances for the method according to the invention. However, they can also be prepared from other modified bacteriochlorophylls according to the invention.

The compounds I to XII fall under the general formula I. The compounds XIII and XIV that are shown in the table fall under the general formula IIIa or IIa.

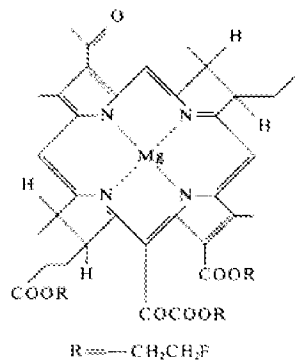
Table

No.	Compound	R ₁	R ₂	R ₃
I	bacteriochlorophyll a	phythl	COOCH ₃	H
II	13 ² -hydroxy-bacteriochlorophyll a	phythl	COOCH ₃	OH
III	pyro-bacteriochlorophyll a	phythl	H	H
IV	II-ethyl ester	C ₂ H ₅	COOCH ₃	OH
V	II-trifluorobutyl ester	(CH ₂) ₃ —CF ₃	COOCH ₃	OH
VI	II-sorbityl ester	sorbitol	COOCH ₃	OH
VII	II-O-serinyl ester	serine	COOCH ₃	OH
VIII	II-amino hexyl ester	(OH ₂) ₆ —NH ₂	COOCH ₃	OH
IX	gamma-globulin derivative of VIII	(CH ₂) ₆ —N—GG [*]	COOCH ₃	OH
X	II-pentaoxyethylene ester	(CH ₂ CH ₂ O) ₅ —H	COOCH ₃	OH
XI	ethylene glycol-bis-bacteriochlorophyll	CH ₂ CH ₂ —O—II	COOCH ₃	OH
XII	1-methyl ester	CH ₃	COOCH ₃	H

^{*}) GG = gamma-globulin



(XIII) 13¹-a-oxa-13²-oxo-bacteriochlorophyll a-fluoroethyl ester



(XIV) bacteriochlorine -e₆-tris-fluoroethyl ester

The examples explain the invention.

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Example 1

Preparation of 13²-hydroxy-bacteriochlorophyllide a-ethyl ester (IV)

30 mg of the compound II, which is listed in the above table, are dissolved in 30 ml of a 2 percent ethanolic sodium hydroxide solution under argon and stirred for 15 minutes. Then the reaction mixture is treated with a mixture of diethyl ether and water. The organic phase is removed, washed until neutral, and dried with sodium chloride and liberated of the solvent under reduced pressure. The compound IV is obtained in a yield ranging from 80 to 90% of the theory. The structure of the compound is determined by NMR and mass spectroscopy.

Example 2

Preparation of Compound V

In a two neck flask with a drying tube 30 mg of the solid compound II are mixed with an anhydrous and oxygen-free solution of 0.5 g of diazabicycloundecane in 2 ml of 4,4,4-trifluorobutane-1-ol under argon and stirred at 65°C for 1 hour. The reaction mixture is processed in the same way as in example 1. The compound V is obtained in a yield of 40% of the theory. Its structure is determined by NMR and mass spectroscopy.

Example 3

Preparation of Compound X

The compound X is prepared according to example 1. In this case, pentaerythritol is used as the alcohol; and dioxan is used as the solvent.

Example 4

Preparation of Compound XII

The compound XII is prepared according to example 1. In this case, the compound I is used as the parent substance and methanol is used as the alcohol component. The reaction time is only 2 minutes.

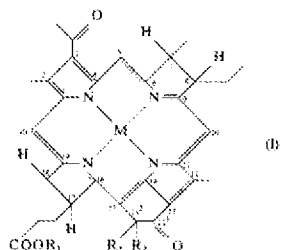
Example 5

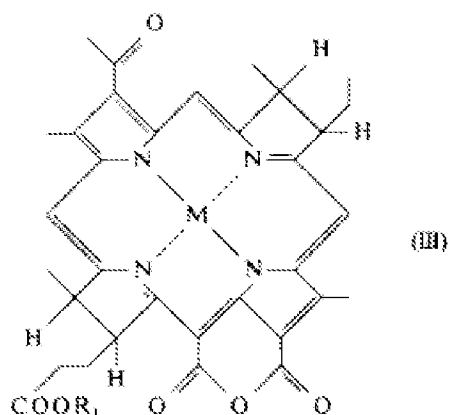
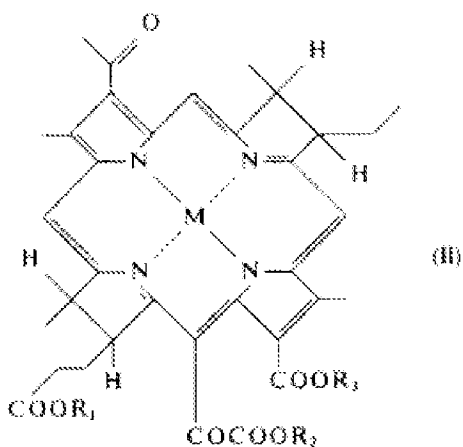
Preparation of Compound XIII

The compound XIII is prepared according to example 4, but in this case, 2-fluoroethanol serves as the alcohol component. The reaction time is 1 hour. The compound XIII is obtained with a yield of 20%.

Patent Claims

1. Modified bacteriochlorophylls of the general formula I, II, or III





where

M denotes a hydrogen or a metal atom,

R₁ denotes an oligooxyethylene glycol residue or a residue of an unbranched or branched aliphatic or a cycloaliphatic, optionally halogenated, alcohol having at least 3 carbon atoms or a residue of a hydroxylated amino acid, a sugar alcohol, a hydroxylated lipid, a linear polyol, an amino alcohol, a hydroxycarboxylic acid, a nitroxide group containing alcohol, an alcohol containing chromophoric residues or an alkylbenzyl alcohol,

R₂ denotes a hydrogen atom, a hydroxyl group or a residue of the general formula -COOR₄, where R₄ denotes an alkyl or cycloalkyl residue having 1 to 12 carbon atoms, and

R₃ denotes a hydrogen atom, a hydroxyl group or an alkyl or alkoxy residue having 1 to 12 carbon atoms, where R₂ and R₃ can also be identical.

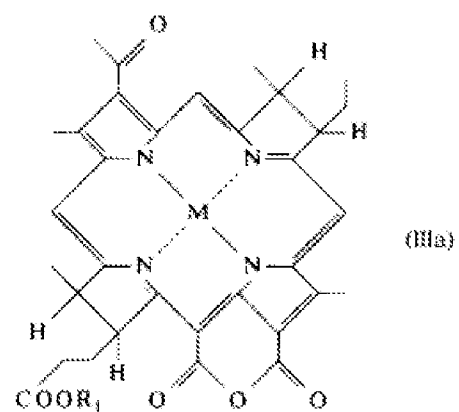
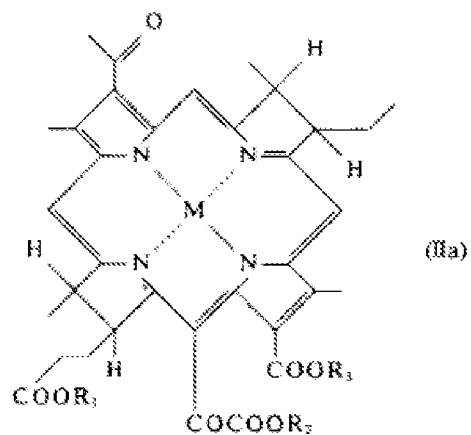
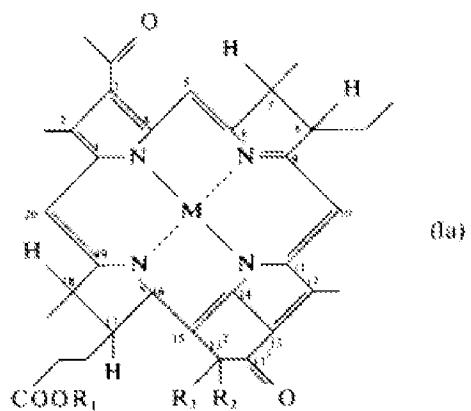
2. Modified bacteriochlorophylls, as claimed in claim 1, characterized in that M denotes, as the metal atom, a magnesium, zinc, nickel, copper or tin atom in the general formula I, II or III.

3. Modified bacteriochlorophylls, as claimed in claim 1 or 2, characterized in that in the general formula I, II or III the R₁ residue denotes a fluoroethyl, trifluorobutyl, sorbityl, O-serinyl, aminohexyl or pentaoxyethylene glycol group.

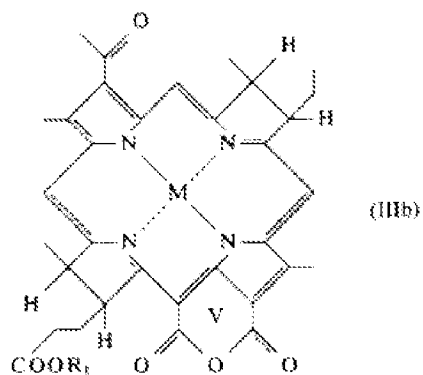
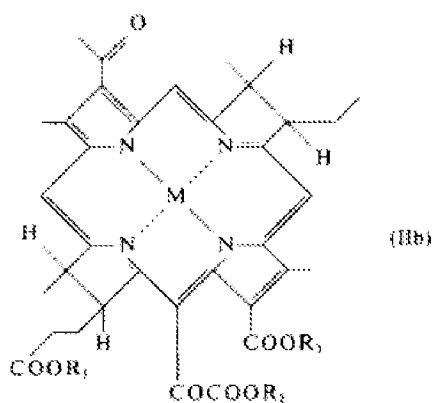
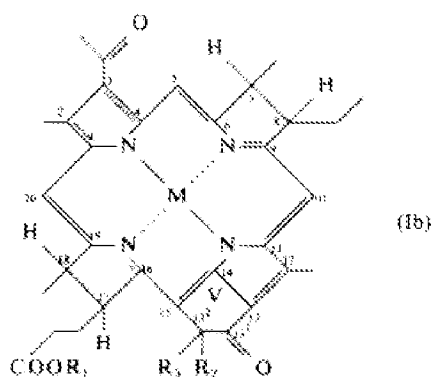
4. Modified bacteriochlorophylls, as claimed in any one of the claims 1 to 3, characterized in that in the general formula I or II the R₂ residue denotes the -COOCH₃ group.

5. Modified bacteriochlorophylls, as claimed in any one of the claims 1 to 4, characterized in that in the general formula I or II the R₃ residue denotes a hydroxyl group.

6. Method for preparing modified bacteriochlorophylls of the general formula Ia, IIa or IIIa



where M, R₁, R₂ and R₃ have the same meaning as disclosed in claim 1, but in addition R₁ can also denote a methyl, ethyl, ethylene glycol or phytyl group or a residue of a diterpene alcohol, characterized in that a bacteriochlorophyll of the general formula Ib, IIb or IIIb



where M, R₁, R₂ and R₃ have the same meaning as given above for the general formulas Ia, IIa and IIIa, and where V in the general formulas Ib and IIIb denotes a ring in the total structure of the bacteriochlorophyll, in the presence of a base as well as in the presence or absence of an inert solvent and/or a stoichiometric excess of one of the two reaction partners with at least one alcohol in the form of phytol or oligooxyethylene glycol or an unbranched or branched aliphatic or cycloaliphatic, optionally halogenated, alcohol or in the form of a hydroxylated amino acid, a sugar alcohol, a hydroxylated lipid, a linear polyol, an amino alcohol, a hydroxycarboxylic acid, a nitroxide group containing alcohol, an alcohol containing chromophoric residues, an alkylbenzyl alcohol having 1 to 12 carbon atoms in the alkyl residue or a diterpene alcohol on the propionic acid residue, which is bonded to the carbon atom C-17 of the bacteriochlorophyll, is transesterified and the resulting modified bacteriochlorophyll is isolated from the reaction mixture.

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7. Method, as claimed in claim 6, characterized in that the parent compound that is used is a bacteriochlorophyll of the general formula Ib, IIb or IIIb, where M denotes, as the metal atom, a magnesium, zinc, nickel, copper or tin atom.

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8. Method, as claimed in claim 6 or 7, characterized in that the parent compound that is used is a bacteriochlorophyll of the general formula Ib, IIb or IIIb, where R_1 denotes a fluoroethyl, trifluorobutyl, sorbityl, O-serinyl, aminohexyl or pentaoxyethylene glycol group.
9. Method, as claimed in any one of the claims 6 to 8, characterized in that the parent compound that is used is a bacteriochlorophyll of the general formula Ib or IIb, where R_2 denotes the $-\text{COOCH}_3$ group.
10. Method, as claimed in any one of the claims 6 to 9, characterized in that the parent compound that is used is a bacteriochlorophyll of the general formula Ib or IIb, where R_3 denotes a hydroxyl group.
11. Method, as claimed in any one of the claims 6 to 10, characterized in that the alcohol that is used as the reaction partner is a methanol, ethanol, ethylene glycol, 2-fluoroethanol, 4,4,4-trifluorobutane-1-ol, sorbitol, serine, aminohexanol or pentaoxyethylene glycol.
12. Method, as claimed in any one of the claims 6 to 11, characterized in that the base that is used is a hydroxyl ion-forming compound, a Lewis base or an organic base.
13. Use of the modified bacteriochlorophylls, as claimed in any one of the claims 1 to 5 and use of the modified bacteriochlorophylls, obtained according to any one of the claims 6 to 12, for the preparation of agents for the diagnosis or treatment of tumors.

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